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Investigation of the effect Of FSH/LH Ratio on pregnancy success before IVF in infertile patients

FSH/LH value affects pregnancy outcomes

Tuğçehan Şimşekler[1], Mehmet Cengiz Çolakoğlu[2], Sevcan Sarıkaya[1]
[1] Department of Obstetrics and Gynecology, Konya City Hospital
[2] Department of Obstetrics and Gynecology, Faculty of Medicine, Necmettin Erbakan University, Konya, Türkiye

Abstract

Aim: In our study, we investigated the effect of FSH/LH ratio on pregnancy success before in vitro fertilization (IVF) and its success in predicting ovarian response.

Material and Methods: This study includes a total of 265 patients who applied to our clinic for various infertility reasons and underwent in vitro fertilization embryo transfer (IVF-ET) treatment between January 2018 and December 2021. The study data were obtained by retrospectively examining patients' files. A total of 265 patients were included in the study, including 211 patients with early follicular phase FSH/LH<2 (Group I) and 54 patients with FSH/LH ≥2 (Group II). The adopted parameters were statistically compared between the groups in terms of treatment characteristics and ovarian stimulation results, gonadotropin initial dose, treatment stimulation time, total dose of gonadotropin used, number of oocytes collected, number of developing embryos, estrogen value on OPU (oocyte pick-up) day, endometrial thickness on OPU day, and progesterone value on day 12. The parameters were also statistically compared between the groups in terms of pregnancy outcomes, the number of biochemical pregnancies, clinical pregnancies and live births. Patients with an FSH value of 11 IU/L and above, the patient's age over 40, the patient's diagnosis of polycystic ovary syndrome, and the cancellation of embryo transfer for any reason were excluded from the study.

Results: In our study, as a result of controlled ovarian hyperstimulation, the estrogen level on the day of OPU and the total number of oocytes collected were found to be statistically higher in the group with low FSH/LH ratio. There was no statistical difference between the groups in terms of the starting dose of gonadotropin used, the total dose of gonadotropin used, the endometrial thickness measured on the day of OPU, the duration of stimulation, the number of developing embryos and the progesterone value on the 12th day. The biochemical pregnancy, clinical pregnancy and live birth rates of the patients after IVF-ET treatment were similar in both groups, and no statistically significant difference was observed. In patients with normal FSH values, a negative correlation was observed between the FSH/LH ratio and the estrogen level on the day of OPU and the total number of oocytes collected. The data obtained; It means that a low-response ovarian response may occur as a result of controlled ovarian hyperstimulation in the group with a normal FSH value and an FSH/LH ratio of 2 or more. However, pregnancy rates were similar in both groups.

Discussion: We see that the FSH/LH ratio does not have a negative effect on the rate of conception as a result of IVF. However, we think that an FSH/LH ratio of 2 and above may be one of the parameters that can be used to predict poor ovarian response in patients.

Keywords

Infertility, FSH/LH Ratio, Ovarian Reserve

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Corresponding Author: Tuğçehan Şimşekler, Department of Obstetrics and Gynecology, Konya City Hospital, Konya, Türkiye.
E-mail: tugcehnn@gmail.com P: +90 543 714 25 51
Corresponding Author ORCID ID: https://orcid.org/0000-0003-1767-2383
Other Authors ORCID ID: Mehmet Cengiz Çolakoğlu, https://orcid.org/0000-0003-4518-6016 · Sevcan Sarikaya, https://orcid.org/0000-0002-0922-4671
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Introduction

Infertility is defined as the inability of couples to achieve pregnancy after at least one year of unprotected sexual intercourse. Among couples in the reproductive period, it affects 15-20% [1]. Evaluation and treatment can be done without waiting for 1 year, depending on the anamnesis and clinical findings [2]. In women aged 35 and over, those with menstrual irregularity, those with a history of pelvic pathology or endometriosis, and those with a known male factor, investigation should be started as soon as possible [3].

The main causes of infertility are pathologies related to the tuba, ovulation disorders, and male factor [4]. Causes of male origin from the most common to the least common include idiopathic, primary gonadal pathologies, sperm transport pathologies and hypothalamic - pituitary pathologies [5]. The most common to the least common causes of female origin include tubal and pelvic pathology, ovulatory dysfunction and rare problems [6]. As a result of the investigation of infertile couples In 15%, no demonstrable cause can be identified and this is defined as unexplained infertility [7].

Achieving a successful pregnancy depends on endometrial development in both normal and stimulated cycles, follicle development as a result of adequate ovarian reserve, and its compatibility with embryo quality [8]. While the ovarian reserve reflects the reproductive capacity of a woman in the reproductive period as a result of the amount of oocyte she has; decreased ovarian reserve, on the other hand, decreased response and fecundity of a woman of reproductive age with regular cycles to ovarian stimulation compared to women in the same age group. In other words, it is clinically defined as the decrease in the probability of obtaining a live birth as a result of a menstrual cycle [9]. Patients with low ovarian reserve constitute a significant portion of the patients who receive IVF treatment.

The basal follicle stimulating hormone (FSH) level on the 3rd day of the menstrual cycle is one of the most commonly used tests for ovarian reserve [10]. Although the basal FSH level is within the normal range, some patients have insufficient ovarian stimulation. This group of patients, around ten percent of whom did not develop adequate follicles as a result of the treatment, was named as "poor ovarian responder" [11]. In these patients, more cycle cancellations, less follicle development, low or slowly increasing E2 levels and low pregnancy rates are monitored [12]. With reproductive aging, serum FSH levels increase, and in the next step, luteinizing hormone (LH) levels also increase [13]. As a result, the increase in the FSH/LH ratio with normal FSH levels on the third day of the menstrual cycle may be a determinant of ovarian reserve and poor ovulation results [14]. An increase in the FSH/LH ratio of two or more and an increase in sex hormone binding (SHBG) levels impair oocyte quality and reduce implantation success [15].

In our study, we aimed to investigate the effect of controlled ovulation hyperstimulation cycles between groups with two or more FSH/LH ratios and less than two groups on pregnancy outcomes and their success in predicting ovarian response.

Material and Methods

In this study, a total of 329 patients, who applied to IVF and subsequently ET (embryo transfer) between January 2018 and December 2021, applied to the IVF Unit due to infertility data has been reached. Patients with an FSH value of 11 IU/ml and above, patients over the age of 40, patients with PCOS due to infertility, and patients whose embryo transfer was canceled for any reason were not included in the study. 64 patients were excluded from the study.

The patient files were scanned retrospectively, and the patients' age, early follicular phase (2nd or 3rd day of menstrual cycle), FSH, LH, E2 values, whether the mother was smoking or not, and the causes of infertility were noted. Patients whose histories were taken at the first admission, physical examination and pelvic examination were performed and recorded in their files were included in the evaluation. The endometrial cavity, ovaries and tuba of each patient included in the evaluation were evaluated by ultrasonography and hysterosalpingography. The diagnosis of decreased ovarian reserve is defined for patient groups in which AMH is <0.5-1.1 ng/mL or in which the total number of antral follicles in both ovaries is counted as <7-10 by tvusg performed on the 3rd day of the cycle. The male factor was evaluated according to the criteria of the World Health Organization by spermiogram. All of our work was carried out with a fresh cycle.

The patients included in the study were divided into 2 groups, 211 patients with FSH/LH<2 (Group I) and 54 patients with FSH/LH ≥2 (Group II), according to the early follicular phase FSH/LH ratio. Between the two groups, the number of oocytes collected, the number of embryos formed, the ET (endometrial thickness) value on the oocyte pick up (OPU) day, the estrogen value on the OPU day, the progesterone value on the 12th day after embryo transfer, the initial and total gonadotropin dose, biochemical pregnancy, clinical pregnancy and live birth rates were compared. Biochemical pregnancy is the occurance of miscarriage following increased blood B-hCG level (>20 mIU/ml). Clinical pregnancy was recorded when a gestational sac was visible on ultrasonography at the 6th week, and live birth was recorded for pregnancies that continued beyond the 23rd week.

Statistical Analysis

SPSS version 22 (SPSS Inc., Chicago, IL) was used for statistical analysis. Whether the values of both groups showed normal distribution was evaluated with Kolmogorov Smirnov, Shapiro-Wilk test and histograms. Normally distributed data were evaluated with the independent t test. Categorical data of both groups were compared with Chi-square test. P value below 0.05 was considered statistically significant.

Ethical Approval

This study was approved by Necmettin Erbakan Unıversity Ethıcs Commıttee For Non-Drug and Non-Medical Device Research (Date: 2022-04-15, No:2022/3748).

Results

The mean age of the patients included in the study was 31, the mean BMI was 25.4, the mean basal FSH value was 6.3 IU/L, the mean basal LH value was 5.5 IU/L, and the mean basal E2 value was 43.1 pg/ml. Demographic data and hormonal values were compared between the two groups. There was no significant difference between the groups in terms of age, BMI, basal E2

value, maternal smoking or nulliparity (Table 1).

When the two groups were compared in terms of infertility etiology, no significant difference was found between the groups in terms of tubal factor, endometriosis, male factor, decreased ovarian reserve and unspecified factor. Infertility due to uterine factor was found to be statistically significantly higher in Group2 (p=0.008). The groups were compared in terms of treatment characteristics and ovarian stimulation results (Table 2). Gonadotropin starting dose (271.2±58.5 IU/L) and total dose (2631.7±770.8 IU/L) used for controlled ovarian hyperstimulation in Group I were observed. There was no significant difference between the two groups in terms of gonadotropin doses. The total number of oocytes collected in the OPU procedure (9.7±5.2 vs. 8.1±5.1; p=0.049) and the estrogen level on the day of OPU (1901.6±1178.5 vs. 1407.7±1033.5 ; p=0.005) were found to be statistically significantly higher in Group I. The results are shown in Figure 1 and Figure 2, respectively. There was no statistically significant difference between the groups in terms of Endometrial thickness (10.3±2.3 vs. 9.9±2.4 mm), stimulation time (9.7±2.1 vs. 9.3±1.9 days), number of developing embryos (2.7±1.6 vs. 2.8±2.0) and progesterone value on day 12 (21.4±23.2 vs. 23.8±24.9ng/ml). GnRH antagonist protocol 164(77.7%) vs. 36(66.7%), while the GnRH agonist protocol is 47(22.3%) vs 18(33.3%), no statistically significant difference was observed between the groups in terms of the preferred protocol.The data of the patients in terms of pregnancy outcomes after IVF-ET treatment are analyzed in Table 3. Biochemical pregnancy rate was 18(8.5%) and 8(14.8%) in Group I and Group II,

Table 1. Comparison of demographic data and hormonal values of the groups

	Group I (FSH/LH <2) N=211	Group II (FSH/LH ≥2) N=54	P value
Age*	31.1±4.9	32±4.7	0.247
Bmi*	25.7±5.3	24.2±4.5	0.056
Basal Fsh (D2,3 mIU/mL) *	6.1±2.5	6.8±2.7	0.051
Basal Lh (D2,3 mIU/mL)*	6.2±2.3	2.8±1.5	<.001
Basal E2 (D2,3 pg/mL)*	42±25.5	48.1±29.2	0.139
Maternal smoking**	16(7.6%)	4(7.4%)	0.965
Nulliparity**	156(73.9%)	41(75.9%)	0.765

Values are given as mean±standard deviation, n(%). P value was obtained by Chi-square test** and independent t test*.

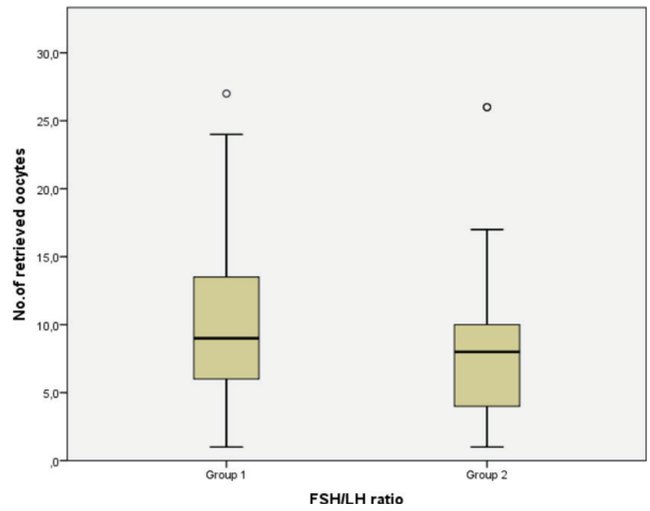

Figure 1. Comparison of the number of collected oocytes between groups

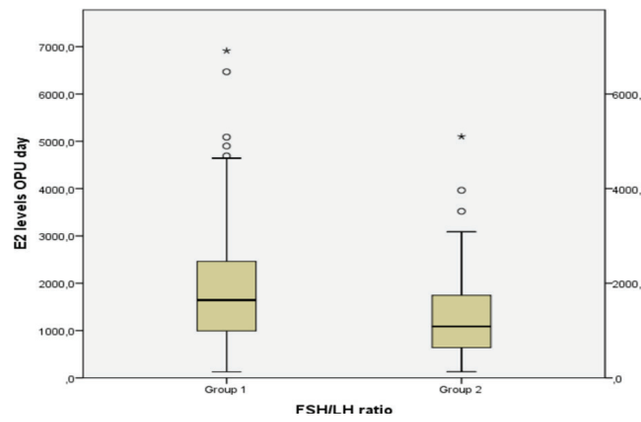

Figure 2. Comparison of Estrogen level on OPU day between groups

Table 3. Comparison of the groups in terms of pregnancy outcomes

	Group I (FSH/LH <2) N=211	GroupII (FSH/H≥2) N=54	P value
Biochemical Pregnancy	18(8.5%)	8(14.8%)	0.166
Clinical Pregnancy	55(26.1%)	15(27.8%)	0.799
Live Birth	35(16.6%)	7(13%)	0.515

Values are given as n(%). P value was obtained by Chi-Square test.

Table 2. Comparison of the groups in terms of treatment characteristics and ovarian stimulation results

	Group I: (FSH/LH <2) N=211	Group II: (FSH/LH ≥2) N=54	P value
Estrogen Level On The Day of OPU*	1901.6±1178.5	1407.7±1033.5	0.005
Endometrial Thickness (mm)*	10.3±2.3	9.9±2.4	0.221
Gonadotropin Starting Dose (IU/L)*	271.2±58.5	283.3±59.4	0.177
Stimulation Days *	9.7±2.1	9.3±1.9	0.191
Gonadotropin Total Dose (IU/L)*	2631.7±770.8	2675.0±907.9	0.723
No. of Retrieved Oocytes*	9.7±5.2	8.1±5.1	0.049
No. of Embryos on ET Day*	2.7±1.6	2.8±2.0	0.638
Progesterone Value on Day 12 ng/ml *	21.4±23.2	23.8±24.9	0.516
GNRH Antagonist Protocol**	164(77.7%)	36(66.7%)	0.092
GNRH Agonist Protocol**	47(22.3%)	18(33.3%)	

Values are given as means±standard deviations, n(%). P value was obtained by Chi -Square test**, independent t test*. Significant p values are given in boldface

clinical pregnancy rates 55(26.1%) and 15(27.8%), live birth rates 35(16.6%) and 7(13%) was calculated as. There was no statistically significant difference between the groups in terms of results.

Discussion

FSH is required for folliculogenesis, but the final stages of maturation are optimized by LH [16]. The presence of LH prior to ovulation is essential for optimal follicular development, ultimately resulting in a healthy oocyte [17]. When the follicle reaches 10–12 mm, LH receptors develop on the granulosa cells [18]. Early follicular phase hormonal measurements (FSH, AMH, inhibin B, E2) are used as ovarian reserve tests. Even patients of the same age have different ovarian responses in the IVF cycle. Today, the importance of predicting treatment results has increased with the increase in the frequency of infertility and the frequency of ART (Assisted Reproductive Techniques). The factors affecting the successful outcome of IVF-ICSI treatment have been tried to be revealed by some studies [19-21]. Several previous studies with gonadotropins have shown that early follicular phase FSH/LH rate predicted low-response ovarian stimulation and low pregnancy outcomes [22-24]. In this study, we investigated the effect of early follicular phase FSH/LH ratio on pregnancy outcome and its success in predicting ovarian response in patients who underwent IVF-ICSI-ET.

In a study by Eman Shaeer et al., patients were divided into two groups as FSH/LH ratio < 2 and FSH/LH ratio ≥ 2, and no significant difference was observed between the groups in terms of total gonadotropin dose used throughout the IVF cycle. At the same time, no significant difference was observed in terms of the number of oocytes collected and embryo quality, and clinical pregnancy rates. FSH/LH ratio was not found to be significant in terms of IVF results [20]. In our study, no statistically significant difference was observed between the groups in terms of gonadotropin doses, number of developing embryos and clinical pregnancy rates. However, the number of oocytes collected after OPU was found to be significantly higher in Group I.

Mukherjee et al. [21] In a retrospective study conducted by A.Ş., it was shown that the ovarian response decreased when the FSH/LH ratio was above 3.6 in those under the age of 41 with an FSH value of less than 15 IU/L. It is seen that this ratio starts to increase before the increase in FSH. In our study, low-response ovarian response was found in the group with an FSH/LH ratio of 2 and above. Lenton et al. [13] showed in their study that the increase in FSH value occurs a few years before the increase in LH, and they stated that the FSH/LH ratio is probably one of the earliest signs of decreased ovarian reserve. In our study, the number of oocytes collected (9.7±5.2 vs. 9.3±1.9; p= 0.049) and the estrogen level on the OPU day (1901.6±1178.5 vs. 1407.7±1033.5 pg/ml; p=0.005) were found in the group with low FSH/LH ratio(Group I) was over-monitored with statistical significance. This situation can be associated with low ovarian response for Group II.

Liu et al. [22] compared two groups with normal and increased FSH/LH values in terms of cycle characteristics and results. They found that patients in the group with an increased FSH/LH ratio probably had a higher initial dose (257 vs. 232 IU) and total dose of gonadotropin (2484 vs. 2136 IU) with a more aggressive protocol. Cycle cancellation rates were higher in the group with increased FSH/LH ratio. Again, the rate of pregnancy in this group although lower (24.7% vs. 33.5%) was observed, no statistically significant difference was shown. In our study, the initial and total dose of gonadotropin was 271.2±58.5 vs. 283.3±59.4, 2631.7±770.8 etc. It was calculated as 2675.0±907.9 and it was observed higher in Group II. However, no statistically significant difference was observed.

Sang Woo Lyu et al. [23], compared two groups with FSH/LH < 2 and FSH/LH ≥ 2 in terms of number of retrieved oocytes and mature oocytes, implantation rate, clinical pregnancy, and ongoing pregnancy rates. Women with high FSH/LH ratios have subclinically low ovarian reserve and low pregnancy rates as a result of IVF. Similarly, Prasad et al. [24] included 105 patients undergoing COH for IVF treatment in their study. In the retrospective study, patients were divided into two groups as FSH/LH≥2 and FSH/LH<2. It was shown that higher doses of gonadotropin (3019.34 and 2482.43 IU) were used throughout the cycle in women in the group with an FSH/LH≥2 (n=31) ratio. It was also shown that this group developed fewer mature follicles (>16 mm), retrieved fewer oocytes, and had a lower pregnancy rate (11.1% vs. 33.8%). In conclusion, they associated increased FSH/LH ratio with decreased ovarian response and lower IVF success rate. Rehana Rahman et al. [25] showed that low FSH/LH ratio is associated with good oocyte parameters, quality embryo and high implantation rate. In our study, clinical pregnancy rates were n=55(26.1%) vs. 15=(27.8%) and no significant difference was observed.

Conclusion

We see that the FSH/LH ratio does not have a negative effect on the rate of conception as a result of IVF. However, we think that an FSH/LH ratio of 2 and above in patients undergoing controlled ovarian stimulation may be one of the parameters that can be used to predict poor ovarian response.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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